ORIGINAL ARTICLE

Comparison of Ximelagatran with Warfarin for the Prevention of Venous Thromboembolism after Total Knee Replacement

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ABSTRACT

BACKGROUND

In a previous study of the prevention of venous thromboembolism after total knee replacement, the efficacy of ximelagatran, an oral direct thrombin inhibitor that does not require monitoring of coagulation or dose adjustment, was found to be similar to that of warfarin at a dose of 24 mg of ximelagatran twice daily. The purpose of the present study was to determine whether a higher dose of ximelagatran is superior to warfarin.

METHODS

This randomized, double-blind trial compared a regimen of 7 to 12 days of oral ximelagatran, at a dose of 24 or 36 mg twice daily, starting the morning after surgery, with warfarin therapy started the evening of the day of surgery. The composite end point of venous thromboembolism and death from all causes and the incidence of bleeding were the primary outcome measures.

RESULTS

Among the 1851 patients in the efficacy analysis, oral ximelagatran at a dose of 36 mg twice daily was superior to warfarin with respect to the primary composite end point of venous thromboembolism and death from all causes (20.3 percent vs. 27.6 percent; P=0.003). There were no significant differences between these two groups with respect to major bleeding (incidence, 0.8 percent and 0.7 percent, respectively), perioperative indicators of bleeding, wound characteristics, or the composite secondary end point of proximal deep-vein thrombosis, pulmonary embolism, and death (2.7 percent vs. 4.1 percent; P=0.17).

CONCLUSIONS

The efficacy of oral ximelagatran, administered starting the morning after total knee replacement, was superior to that of warfarin for prevention of venous thromboembolism. Rates of hemorrhagic complications with the two drugs were similar.

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*The members of the EXULT A (Exanta Used to Lessen Thrombosis A) Study Group are listed in Supplementary Appendix 1, available with the full text of this article at http://www.nejm.org.

ENOUS THROMBOEMBOLISM OCCURS
in 40 to 84 percent of patients who under-
go total knee replacement and do not re-
ceive prophylactic drugs; in 9 to 20 percent of these
patients the thrombosis is proximal,[1] up to 7 per-
cent have a pulmonary embolus,[2,3] and in 0.2 to 0.7
percent the embolus is fatal.[4-6] Prophylaxis with ei-
ther warfarin or low-molecular-weight heparin is
widely used in North America.[1] Nevertheless, ap-
proximately 47 percent of patients treated with war-
farin and 31 percent of those treated with low-
molecular-weight heparin have thrombosis after
total knee replacement.[1] Warfarin has a slow onset
of action, interacts with numerous foods and drugs,
and requires monitoring of coagulation and dose
adjustment. The low-molecular-weight heparins
must be given parenterally, and they are associated
with a higher rate of bleeding at the surgical site than
is warfarin, especially if heparin therapy is started
soon after surgery.[1]

Ximelagatran is an orally administered direct
thrombin inhibitor under development as an anti-
coagulant agent for prophylaxis against and treat-
ment of thromboembolism. It is rapidly absorbed
and quickly converted into its active form, melagat-
ran, a reversible, active-site inhibitor of both free
and clot-bound thrombin[7] that has stable and re-
producible pharmacokinetic properties. No clini-
cally relevant interactions with food or cytochrome
P-450–metabolized drugs have been reported with
ximelagatran.[8-13] Initial studies have shown ximel-
agatran to have good efficacy and safety in the pre-
vention of venous thromboembolism after total
knee or total hip replacement.[14-17] Results of a
phase 2 trial[15] suggested a wide range of doses with
good efficacy and safety, and an initial phase 3 trial
showed that treatment with ximelagatran at a dose
of 24 mg twice daily was at least as effective as war-
farin.[14] The purpose of the present study was to de-
termine whether a higher dose would be safe and
more effective than warfarin.

METHODS

STUDY DESIGN
We conducted a prospective, randomized, double-
blind trial at 116 centers in the United States, Cana-
da, Israel, Mexico, and Brazil. The institutional re-
view board at each center approved the protocol, and
written informed consent was obtained from all pa-
tients before any study procedures were conducted.
The study was conducted in accordance with the
ethical principles stated in the Declaration of Hel-
sinki. Patients were screened 1 to 30 days preoper-
atively, and they were randomly assigned after post-
operative rescreening to receive ximelagatran at a
dose of 24 mg twice daily, ximelagatran at a dose of
36 mg twice daily, or warfarin. Randomization was
performed with the use of a computer-generated
system, with stratification at each center according
to whether patients underwent unilateral or bilater-
al surgery.

PATIENTS
Eligible patients were women without childbearing
potential and men who weighed between 40 and
136 kg. Only patients undergoing primary total knee
replacement were included. The criteria for exclu-
sion were pneumatic leg compression; immobiliza-
tion for 3 or more days; major surgery, stroke, myo-
cardial infarction, or receipt of any investigational
drug within 30 days before surgery; intracranial, ret-
roperitoneal, or intraocular bleeding or any other
disorder associated with an increased risk of bleed-
ing within 90 days before surgery; gastrointestinal
bleeding within 90 days before surgery, ulcer disease
verified by endoscopic examination within 30 days
before surgery, or both; uncontrolled hypertension;
cancer that required cytostatic treatment or was it-
self the reason for total knee replacement; an ala-
nine or aspartate aminotransferase level greater
than two times the upper limit of the normal range;
thrombocytopenia; drug or alcohol abuse within
the previous 6 months; allergy to contrast medium
or iodine; a contraindication to warfarin therapy;
impaired renal function (defined by an estimated
creatinine clearance of less than 30 ml per min-
ute)[18]; and traumatic epidural or lumbar puncture.

If the use of an epidural or spinal catheter con-
tinued into the treatment period, the catheter was
to be removed during trough levels of melagatran
(the active metabolite of ximelagatran). Treatment
with thrombolytic, anticoagulant, or antiplatelet
agents, including heparins, warfarin, direct throm-
bin inhibitors, dipyridamole, sulfinpyrazone, ticlo-
pidine, clopidogrel, acetylsalicylic acid at a dose
greater than 500 mg per day, and dextran, was not
allowed within seven days before surgery or during
the period of administration of the study drug.

TREATMENT REGIMENS
Warfarin (Coumadin, Bristol-Myers Squibb) or a
warfarin placebo was administered each evening,
with the first dose given on the evening of the day of

surgery and with the dose adjusted to achieve an international normalized ratio (INR) of 2.5 (range, 1.8 to 3.0). Ximelagatran at a dose of 24 mg or 36 mg in tablet form (Exanta, AstraZeneca) or a ximelagatran placebo was given in the morning and evening starting 12 hours or more after surgery, when adequate hemostasis had been achieved. The treatment was continued until venography was performed. To guide the adjustment of the warfarin dosage, INR values were measured in a blinded fashion on days 1 to 3 after surgery, on the day when venography was performed, and as needed. INR values were measured either at participating centers, with the use of encrypted point-of-care devices provided by AstraZeneca, or at local laboratories equipped with a system that prevented access to the INR values by local personnel. All INR values were reported to an anticoagulation management center, which relayed real or sham values to local study personnel. A warfarin-dosing nomogram was provided, but the dose of either warfarin or warfarin placebo was chosen at the investigator's discretion. For patients receiving ximelagatran, sham INR values were generated to mimic the usual values in patients receiving warfarin. Compliance with oral treatment was assessed by counting tablets used in the hospital, dispensed at discharge, and returned after the treatment had ended.

ASSESSMENTS OF EFFICACY

The composite primary end point for efficacy comprised total (distal and proximal) deep-vein thrombosis, pulmonary embolism, and death from all causes during treatment, as determined by an independent central adjudication committee. The composite secondary end point for efficacy comprised proximal deep-vein thrombosis, pulmonary embolism, and death from all causes during treatment.

Deep-vein thrombosis was evaluated by means of bilateral ascending venography[19,20] 7 to 12 days after the study treatment was initiated. In addition to central adjudication, venograms were assessed locally by personnel who had no knowledge of the assigned study treatment. The criterion for the diagnosis of deep-vein thrombosis was a consistent intraluminal filling defect on at least two images. To be considered adequate for evaluation, venograms had to show all deep veins except the deep femoral vein, the muscular veins of the calf, and the anterior tibial veins, although these were included in the evaluation if they were visible or if a clot was detected. Venograms were classified as indeterminate if

Table 1. Patients Included in the Analyses, Those Excluded, and Reasons for Exclusion.

Group	Ximelagatran		Warfarin	Total
	36 mg	24 mg		
		no. of patients		
Randomized*	775	762	764	2301
Randomized, not treated	6	5	5	16
Included in safety analysis	769	757	759	2285
Discontinued treatment	53	41	43	137
Adverse events	23	23	13	59
Consent withdrawn	14	8	17	39
Venous thromboembolism confirmed	8	5	4	17
Not eligible	1	1	2	4
Other reasons†	7	4	7	18
No venogram adequate for evaluation and no confirmed symptomatic venous thromboembolism or death‡	140	143	151	434
Venography not performed	89	80	83	252
Indeterminate venogram	55	65	70	190
Included in efficacy analysis	629	614	608	1851

* A total of 355 patients were not randomized for the following reasons: consent was withdrawn (131 patients), eligibility criteria were not fulfilled (106 patients), an adverse event occurred (6 patients), and other reasons (112 patients).
† Other reasons were as follows: an error in the administration of the study medication (two patients in each of the three treatment groups); one or more exclusion criteria were found to apply (two patients in the higher-dose ximelagatran group and two in the warfarin group); the patient was transferred to another facility (one patient in each of the three treatment groups); the treatment assignment was revealed (two patients in the higher-dose ximelagatran group and one in the warfarin group); the patient refused venography because of pain (one patient in the lower-dose ximelagatran group); and the physicians decided to discontinue treatment for an unspecified reason (one patient in the warfarin group).
‡ Four patients in the higher-dose ximelagatran group, two in the lower-dose ximelagatran group, and two in the warfarin group did not have a venogram that was adequate for evaluation but had confirmed symptomatic venous thromboembolism, died, or both.

they showed a lack of filling of a region of the deep-vein system without a filling defect in the same region. Symptomatic proximal deep-vein thrombosis could be diagnosed by compression ultrasonography, but a diagnosis of symptomatic distal deep-vein thrombosis required venography.

A diagnosis of pulmonary embolism was made if a lung scan showed one or more segmental perfusion defects in at least two views with corresponding normal ventilation, if pulmonary angiography showed a persistent intraluminal defect or an abrupt cutoff of a vessel that was greater than 2.5 mm in diameter, if a spiral computed tomographic scan showed a distinct filling defect in a large vessel, if

Table 2. Base-Line Characteristics of Patients Included in the Safety Analysis.*

Characteristic	Ximelagatran		Warfarin (N=759)
	36 mg (N=769)	24 mg (N=757)	
Age — yr	68.5±9.5	67.7±9.7	67.8±9.6
Female sex — no. (%)	492 (64.0)	465 (61.4)	459 (60.5)
Weight — kg	83.9±17.6	84.7±18.0	84.8±17.8
Body-mass index†	30.5±5.6	30.8±5.7	30.6±5.5
Creatinine clearance — ml/min‡	96.1±36.5	99.1±37.8	97.8±39.2
History of venous thromboembolism — no. (%)§	34 (4.4)	29 (3.8)	27 (3.6)
Reason for total knee replacement — no. (%)			
Osteoarthritis	727 (94.5)	717 (94.7)	722 (95.1)
Rheumatoid arthritis	29 (3.8)	31 (4.1)	20 (2.6)
Other	13 (1.7)	9 (1.2)	17 (2.2)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Creatinine clearance rates were estimated on the basis of the Cockcroft–Gault formula.
§ Data include deep-vein thrombosis and pulmonary embolism.

embolectomy was performed, or if a pulmonary embolism was identified on autopsy. Deaths were classified as due to pulmonary embolism or a bleeding event or as not associated with venous thromboembolism or bleeding. All cases of confirmed symptomatic deep-vein thrombosis, suspected pulmonary embolism, and death from any cause were adjudicated centrally. Treatment of confirmed thrombosis was at the discretion of the attending physician.

SAFETY ASSESSMENTS

The primary variables used to assess safety were major bleeding and major or minor bleeding occurring up to 48 hours after the last dose of the study drug had been administered. All bleeding events were reviewed by the independent central adjudication committee and classified as major if they were clinically overt, with one or more of the following findings: involvement of a critical site (intracranial, retroperitoneal, intraocular, intraspinal, or pericardial), a bleeding index of 2.0 or more (calculated as the hemoglobin level [in grams per liter] at the baseline visit minus the postbleeding hemoglobin level, plus the number of units of packed red cells or whole blood transfused), a need for medical or surgical intervention at the operative site, or fatal bleeding. Other episodes of clinically overt bleeding were

classified as minor. The investigators also assessed the appearance and characteristics of the surgical wound (swelling, drainage, erythema, and bleeding) according to the following categories: as expected, better than expected, or worse than expected. Laboratory results were assessed at the time of screening for the study, on the last day of administration of the study drug, and at the follow-up examination four to six weeks after surgery.

STATISTICAL ANALYSIS

We estimated the size of the sample by assuming that the rate of venous thromboembolism with warfarin would be 30 percent and predicting a risk reduction of 33.3 percent with ximelagatran at a dose of 36 mg and of 25 percent with ximelagatran at a dose of 24 mg. To demonstrate these differences at a 5 percent level of significance would require the enrollment of 500 patients per treatment group (for 90 percent power) or 565 patients (for 80 percent power) for the high and low doses of ximelagatran, respectively. We planned to enroll approximately 2250 patients in order to detect a 25 percent risk reduction with the lower dose, given the assumption that 25 percent of venograms would be inadequate for evaluation.

The primary analysis was designed to test the superior efficacy of ximelagatran at a dose of 36 mg twice daily as compared with warfarin. If the difference was significant (as indicated by a two-tailed P value of <0.05), then ximelagatran at a dose of 24 mg twice daily was to be compared with warfarin. The efficacy analyses included all patients who had received at least one dose of a study medication and who had a venogram that was adequate for evaluation or had symptomatic, objectively confirmed deep-vein thrombosis or pulmonary embolism or died during treatment. Bilateral venography was required, but patients undergoing unilateral surgery in whom a clot was detected were included in the efficacy analysis even if a venogram that was adequate for evaluation could be obtained only in the leg that had undergone surgery or only in the contralateral side. For patients who underwent bilateral surgery, venograms that were adequate for evaluation were required in both legs, unless deep-vein thrombosis was found in one leg. Symptomatic venous thromboembolism and deaths that occurred within two days after venography, or up to day 12 if no venography was performed, were included in the analyses.

The frequency of bleeding events was estimated with the use of the observed proportions (with 95

percent confidence intervals) for each treatment group. Differences between each of the two groups receiving ximelagatran and the warfarin group were analyzed with the use of the Cochran–Mantel–Haenszel chi-square test. Differences in blood loss and transfusion requirements were tested with the use of analysis of variance. Differences in ratings of the appearance of the wound and bleeding complications at the surgical site were tested with the use of the Cochran–Mantel–Haenszel chi-square test.

The study was designed by the members of the executive committee of the EXULT A (Exanta Used to Lessen Thrombosis A) Study Group, who also analyzed and interpreted the data. The data were collected by Omnicare Clinical Research at the direction of the executive committee.

RESULTS

STUDY GROUPS

Of 2656 patients who were enrolled, a total of 2301 patients were randomly assigned to a study group and 1851 were included in the analysis of efficacy (Table 1). Of the 450 patients not included, 16 underwent randomization but did not receive treatment; in the case of the remaining 434 patients, the presence or absence of an end point could not be determined because venography either was not performed or was indeterminate or because there was no confirmed symptomatic venous thromboembolic event or death. Base-line characteristics, details of the surgery, and the hospital course were similar in the three groups (Tables 2 and 3). Characteristics of the 2285 patients included in the safety analysis and those of the 1851 patients included in the efficacy analysis did not differ significantly. Venography was adequate for evaluation in 80.7 percent of the patients. In the efficacy analysis, the mean time to the first dose of medication on day 1 was 20.4 hours for all three treatment groups combined; 89 percent of the patients received the assigned study medication for a period of 7 to 12 days. Approximately one third of the patients (701) received additional anticoagulant therapy after discontinuing the study medication at the discretion of the attending physician; in two thirds of these patients (478 patients) the purpose was extended prophylaxis, and in one third (223 patients) it was acute treatment of venous thromboembolism. Only two patients were lost to follow-up; 92 percent of the patients who underwent randomization completed the study, with a follow-up visit at weeks 4 to 6.

Table 3. Characteristics of Knee-Replacement Surgery in Patients Included in the Efficacy Analysis.*

Characteristic	Ximelagatran		Warfarin (N=608)
	36 mg (N=629)	24 mg (N=614)	
Type of surgery — no. of patients (%)			
Unilateral	601 (96)†	593 (97)	585 (96)
Bilateral	27 (4)	21 (3)	23 (4)
Type of anesthesia — no. of patients (%)			
General	285 (45)	271 (44)	288 (47)
Regional	287 (46)	271 (44)	269 (44)
General and regional	57 (9)	72 (12)	51 (8)
Type of prosthesis — no. of patients (%)			
Cemented	564 (90)	557 (91)	546 (90)
Not cemented	14 (2)	15 (2)	21 (4)
Hybrid	51 (8)	42 (7)	41 (7)
Duration of surgery — min	96±34	93±30	96±35
Time to first dose of ximelagatran or ximelagatran placebo — hr	21±4	20±4	20±3
Duration of use of tourniquet — min	75±25	76±26	75±25
Time to ambulation — days	1.6±1.0	1.6±0.9	1.6±1.1
Hospital stay — days‡	6.0±3.0	6.1±3.5	5.8±2.9

* Plus–minus values are means ±SD.
† One patient in the 36-mg group underwent unicompartmental left-knee replacement and arthroscopic surgery.
‡ The hospital stay does not include time spent in a rehabilitation facility.

EFFICACY

The composite primary end point of total venous thromboembolism (deep-vein thrombosis and pulmonary embolism) and death from all causes occurred in 20.3 percent of patients in the group receiving 36 mg of ximelagatran (128 of 629) and in 27.6 percent of patients in the warfarin group (168 of 608) (relative risk reduction, 26.4 percent; P= 0.003) (Table 4). The incidence of the composite primary end point in the group receiving 24 mg of ximelagatran was 24.9 percent (153 of 614 patients; P=0.28 for the comparison with warfarin). Because only unilateral venograms were available for some patients, a sensitivity analysis that included only the patients with bilateral venograms (76.1 percent of the total) was performed, with a similar result. In the 4 percent of patients who had undergone bilateral surgery, the primary end point of total venous thromboembolism or death occurred in 22.2 percent of patients receiving the 36-mg dose of ximelagatran, 19.0 percent of patients receiving the 24-

Table 4. Efficacy and Clinical End Points.*

Event and Study Group	Incidence		Absolute Difference (95% CI)‡	P Value§	Risk Reduction (95% CI)¶
	no./total no.	% (95% CI)†	%		%
Primary end point					
Total venous thromboembolism or death					
Ximelagatran, 36 mg	128/629	20.3 (17.3 to 23.7)	−7.3 (−12.0 to −2.5)	0.003	26.4 (9.9 to 39.8)
Ximelagatran, 24 mg	153/614	24.9 (21.5 to 28.5)	−2.7 (−7.6 to 2.2)	0.28	9.8 (−8.8 to 25.3)
Warfarin	168/608	27.6 (24.1 to 31.4)			
Secondary end point					
Proximal venous thromboembolism or death					
Ximelagatran, 36 mg	17/629	2.7 (1.6 to 4.3)	−1.4 (−3.5 to 0.6)	0.17	34.8 (−19.5 to 64.4)
Ximelagatran, 24 mg	15/606	2.5 (1.4 to 4.0)	−1.7 (−3.7 to 0.3)	0.10	40.3 (−12.1 to 68.2)
Warfarin	25/603	4.1 (2.7 to 6.1)			
Findings on venography					
Total deep-vein thrombosis					
Ximelagatran, 36 mg	124/625	19.8 (16.8 to 23.2)	−7.6 (−12.3 to −2.8)	0.002	27.6 (11.2 to 40.9)
Ximelagatran, 24 mg	151/612	24.7 (21.3 to 28.3)	−2.7 (−7.6 to 2.2)	0.28	9.9 (−8.9 to 25.5)
Warfarin	166/606	27.4 (23.9 to 31.1)			
Proximal deep-vein thrombosis					
Ximelagatran, 36 mg	13/625	2.1 (1.1 to 3.5)	−1.7 (−3.6 to 0.2)	0.07	45.6 (−6.3 to 72.2)
Ximelagatran, 24 mg	12/604	2.0 (1.0 to 3.4)	−1.8 (−3.7 to 0.1)	0.06	48.1 (−3.4 to 73.9)
Warfarin	23/601	3.8 (2.4 to 5.7)			
Distal deep-vein thrombosis					
Ximelagatran, 36 mg	120/625	19.2 (16.2 to 22.5)	−7.5 (−12.1 to 2.8)	0.002	28.0 (11.3 to 41.5)
Ximelagatran, 24 mg	151/612	24.7 (21.3 to 28.3)	−2.0 (−6.9 to 2.9)	0.43	7.4 (−12.1 to 23.6)
Warfarin	161/604	26.7 (23.2 to 30.4)			
Symptomatic events					
Symptomatic venous thromboembolism or death‖					
Ximelagatran, 36 mg	10/769	1.3 (0.6 to 2.4)	0.0 (−1.2 to 1.1)	0.10	
Ximelagatran, 24 mg	8/757	1.1 (0.5 to 2.1)	−0.3 (−1.4 to 0.8)	0.65	
Warfarin	10/759	1.3 (0.6 to 2.4)			

mg dose of ximelagatran, and 34.8 percent of patients receiving warfarin.

The incidence of the combined end point of total venous thromboembolism and death from all causes, on the basis of local interpretation of the venograms, was somewhat higher, but the differences among the groups were similar — 29.6 percent of patients in the higher-dose ximelagatran group (P=0.002 for the comparison with warfarin), 33.4 percent of those in the lower-dose ximelagatran group (P=0.11 for the comparison with warfarin), and 37.7 percent of those in the warfarin group. The superior efficacy of ximelagatran at a dose of 36 mg

was also consistently observed in the analyses of subgroups defined according to age, sex, race or ethnic group, country, weight, body-mass index, creatinine clearance, presence or absence of a history of venous thromboembolism, type of surgery, type of anesthesia, time to the first dose of study medication, and time to ambulation. There were no significant interactions between treatment and these subgroup variables.

The prespecified composite secondary end point of proximal deep-vein thrombosis, pulmonary embolism, and death from all causes occurred in 17 patients (2.7 percent) in the higher-dose ximelagatran

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Table 4. (Continued.)					
Event and Study Group	Incidence		Absolute Difference (95% CI)‡	P Value§	Risk Reduction (95% CI)¶
	no./total no.	% (95% CI)†	%		%
Symptomatic deep-vein thrombosis					
Ximelagatran, 36 mg	7/769	0.9			
Ximelagatran, 24 mg	5/757	0.7			
Warfarin	9/759	1.2			
Pulmonary embolism					
Ximelagatran, 36 mg	2/769	0.3			
Ximelagatran, 24 mg	2/757	0.3			
Warfarin	0/759	0			
Death**					
Ximelagatran, 36 mg	1/769	0.1			
Ximelagatran, 24 mg	1/757	0.1			
Warfarin	1/759	0.1			

* CI denotes confidence interval.
† The exact confidence intervals are provided for within-group estimates.
‡ The difference is the rate in each ximelagatran group (36 mg or 24 mg) minus the rate in the warfarin group.
§ P values were calculated with the use of the Cochran–Mantel–Haenszel test, adjusted for the type of surgery performed (i.e., unilateral or bilateral), and are for the comparison of each ximelagatran group with the warfarin group.
¶ The risk reduction is for each ximelagatran group as compared with the warfarin group. A minus sign indicates an increase in risk.
‖ Data include symptomatic events or deaths (from all causes) that occurred within two days after venography or up to day 12 if no venogram was available. Data are for patients who received at least one dose of the assigned study drug.
** No fatal pulmonary embolism or fatal bleeding event occurred during the treatment period.

group, 15 patients (2.5 percent) in the lower-dose ximelagatran group, and 25 patients (4.1 percent) in the warfarin group (P=0.17 for higher-dose ximelagatran vs. warfarin; P=0.10 for lower-dose ximelagatran vs. warfarin). Slightly more than 1 percent of patients in each group had symptomatic deep-vein thrombosis or died (Table 4).

The INR value was in the target range (1.8 to 3.0) or higher in 65 percent of patients in the warfarin group by postoperative day 3 (mean INR, 2.3) and in 76 percent of patients by the day of venography (mean INR, 2.4). There were no appreciable differences in mean INR values between patients with and those without venous thromboembolism on either day.

SAFETY

Major bleeding occurred during treatment in six patients in each of the two ximelagatran groups and in five patients in the warfarin group (Table 5). Additional major bleeding events occurred during follow-up in four patients in the lower-dose ximelagatran group and in one patient in the warfarin group.

One bleeding complication was fatal; gastric-ulcer bleeding developed in a patient who had received two 36-mg doses of ximelagatran. The bleeding led to multiorgan-system failure and death on day 46. This patient had also received perioperative enoxaparin (as part of the anesthesia protocol) and diclofenac.

Assessment of wound bleeding and of the appearance of the wound revealed no significant differences between either ximelagatran group and the warfarin group (Table 6), and there were no appreciable differences among the groups with respect to other adverse events. The most common postoperative complication was anemia, which occurred in 8 to 10 percent of patients in each of the three groups. Alanine aminotransferase levels were more than three times the upper limit of the normal range in 6 patients in the higher-dose ximelagatran group, 4 patients in the lower-dose ximelagatran group, and 12 patients in the warfarin group on the day of venography and in 4, 1, and 0 patients in the three groups, respectively, at follow-up at four to six weeks (Table 7).

Table 5. Bleeding Events during Treatment in the Patients Included in the Safety Analysis.*			
Bleeding Event	Ximelagatran		Warfarin (N=759)
	36 mg (N=769)	24 mg (N=757)	
Major bleeding — no. (%)	6 (0.8)	6 (0.8)†	5 (0.7)
Any bleeding — no. (%)	41 (5.3)	36 (4.8)	34 (4.5)
Mean operative blood loss — ml (95% CI)	168 (157–180)	169 (157–181)	179 (167–191)
Mean postoperative wound drainage — ml (95% CI)	672 (640–704)	677 (645–710)	682 (650–715)
Mean transfusion volume — ml (95% CI)	224 (199–249)	221 (196–246)	214 (188–239)
Mean bleeding index — 95% CI‡	3.3 (3.2–3.4)	3.3 (3.2–3.4)	3.2 (3.1–3.3)

* For major bleeding and any bleeding, the differences between each ximelagatran group and the warfarin group were not statistically significant. CI denotes confidence interval.

† Symptomatic intracranial bleeding, confirmed by computed tomography on day 6, developed in one patient. A brain biopsy showed that the hemorrhage had occurred in a previously undiagnosed glioma.

‡ The bleeding index was calculated as the hemoglobin level (in grams per deciliter) at the base-line visit minus the hemoglobin level after the bleeding event plus the number of units of red cells transfused.

Table 6. Evaluation of the Surgical Wound.			
Characteristic	Ximelagatran		Warfarin
	36 mg	24 mg	
	no./total no. (%)*		
Wound bleeding			
Unusual bruising, hematoma, or both	31/765 (4.1)	34/754 (4.5)	36/752 (4.8)
Intraarticular bleeding	14/439 (3.2)	10/422 (2.4)	11/405 (2.7)
Wound appearance			
Swelling	43/764 (5.6)	44/753 (5.8)	33/748 (4.4)
Drainage	21/764 (2.7)	20/753 (2.7)	16/748 (2.1)
Erythema	25/764 (3.3)	16/753 (2.1)	28/748 (3.7)
Bleeding	9/764 (1.2)	9/753 (1.2)	9/748 (1.2)
Complications of postoperative treatment			
Wound infection	24/769 (3.1)	20/757 (2.6)	19/759 (2.5)
Abscess	1/769 (0.1)	0	2/759 (0.3)
Wound dehiscence	1/769 (0.1)	2/757 (0.3)	0

* The number is the number of patients in whom a bleeding complication developed or for whom a particular characteristic of the wound was worse than expected as observed at any scheduled visit, including follow-up visits; the total number is the number of patients for whom data were available. None of the differences are statistically significant.

DISCUSSION

Our results show that ximelagatran given orally at a dose of 36 mg twice daily starting postoperatively (a mean of 20.4 hours after surgery) was significantly more effective than warfarin in preventing venous thromboembolism after total knee replacement, with an absolute risk reduction of 7.3 percent and a relative risk reduction of 26.4 percent. The number needed to treat was 14. This benefit was due to a reduction in the rate of asymptomatic deep-vein thrombosis, whereas the rates of proximal deep-vein thrombosis and of symptomatic venous thromboembolism were low in all three treatment groups and did not differ significantly between the group receiving 36 mg of ximelagatran and the warfarin group. Studies of the natural history of venous thromboembolism suggest that asymptomatic deep-vein thrombosis identified by postoperative venography is a predictor of the development of symptomatic venous thromboembolism.[1,21]

As compared with the rates of total and proximal venous thrombosis in seven other multicenter trials of warfarin for prophylaxis after total knee replacement, all conducted in the past 10 years, the rates in our large study (27.4 percent and 3.8 percent, respectively) were among the lowest reported for warfarin. The other studies reported rates of 38 to 55 percent for deep-vein thrombosis and 7 to 12 percent for proximal deep-vein thrombosis.[22-28] The low rates in our study may be related to improvements in general surgical care and to the strict, predefined guidelines used for central adjudication. Also, between two thirds and three quarters of the patients in our study had therapeutic INR values on day 3 and on the day of venography, which is a somewhat higher proportion than usual. Local interpretation of venograms, which was a secondary end point for efficacy, confirmed the superiority of ximelagatran at a dose of 36 mg twice daily, even though the rates of deep-vein thrombosis were higher with local interpretation, most likely because of less stringent application of diagnostic criteria.

The first large, randomized clinical trial of ximelagatran for the prevention of deep-vein thrombosis after total knee replacement in North America showed that a dose of 24 mg twice daily had an efficacy similar to that of warfarin; venous thromboembolism occurred in 19 percent of patients receiving this dose of ximelagatran and in 26 percent of those receiving warfarin (P=0.07).[14] Because the rate of bleeding complications was low and ximela-

gatran was well tolerated over a range of doses, we chose a 36-mg dose, in addition to the 24-mg dose, for our study.

In six studies comparing low-molecular-weight heparin with warfarin after total knee replacement, the rates of venographically identified deep-vein thrombosis in the groups that received low-molecular-weight heparin ranged from 25 percent to 45 percent, with a mean of 31 percent, as compared with rates in the warfarin groups ranging from 38 percent to 55 percent, with a mean of 47 percent.[1,22-27] In one study, which compared fondaparinux, a synthetic pentasaccharide, with enoxaparin in 724 patients, the fondaparinux group had a 12.5 percent rate of thromboembolism, whereas the rate with enoxaparin was 27.8 percent.[29] The incidence of major hemorrhagic complications has been higher with low-molecular-weight heparins than with warfarin.[23-25,27] A meta-analysis of four large clinical trials comparing fondaparinux with enoxaparin for prophylaxis after orthopedic surgery showed that major bleeding was significantly more frequent with fondaparinux.[30]

Warfarin is the single most commonly used pharmacologic form of prophylaxis prescribed after total knee replacement in North America.[31,32] Among the many reasons for this preference are longer experience with the use of warfarin, oral administration, and a lower rate of early bleeding complications than with other agents. Nevertheless, warfarin has a delayed onset of action, requires monitoring of coagulation and dose adjustment, and has multiple interactions with food and drugs.[33,34] The results of our study indicate that fixed-dose ximelagatran, administered without coagulation monitoring, was significantly more effective than warfarin and had similar safety. It could

Table 7. Cumulative Frequency of Elevated Alanine Aminotransferase Values in Patients Included in the Safety Analysis.*

Alanine Aminotransferase	Ximelagatran		Warfarin (N=759)
	36 mg (N=769)	24 mg (N=757)	
	no./total no. (%)		
Base line (before treatment)			
≥3×ULN	0/746	1/731 (0.1)	0/742
≥5×ULN	0/746	1/731 (0.1)	0/742
≥7×ULN	0/746	0/731	0/742
Day of venography (end of treatment)			
≥3×ULN†	6/718 (0.8)	4/697 (0.6)	12/697 (1.7)
≥5×ULN	2/718 (0.3)	1/697 (0.1)	2/697 (0.3)
≥7×ULN	0/718	0/697	1/697 (0.1)
Follow-up visit (4–6 wk)			
≥3×ULN‡	4/700 (0.6)	1/693 (0.1)	0/700
≥5×ULN	1/700 (0.1)	0/693	0/700
≥7×ULN	0/700	0/693	0/700

* ULN denotes upper limit of normal.
† All patients in this category had normal levels at the follow-up visit.
‡ On follow-up testing, the levels were normal in all patients in this category except one. The exception was a patient in the group receiving 36 mg of ximelagatran from whom the investigator was able to obtain only an initial sample.

therefore be considered as an alternative to other available thromboprophylactic agents.

REFERENCES

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. Chest 2001;119:Suppl 1:132S-175S.
2. Stulberg BN, Insall JN, Williams GW, Ghelman B. Deep-vein thrombosis following total knee replacement: an analysis of six hundred and thirty-eight arthroplasties. J Bone Joint Surg Am 1984;66:194-201.
3. Stringer MD, Steadman CA, Hedges AR, Morley TR, Kakkar VV. Deep vein thrombosis after elective knee surgery: an incidence study in 312 patients. J Bone Joint Surg Br 1989; 71:492-7.
4. Mohr DN, Silverstein MD, Ilstrup DM, Heit JA, Morrey BF. Venous thromboembolism associated with hip and knee arthroplasty: current prophylactic practices and outcomes. Mayo Clin Proc 1992;67:861-70.

5. Khaw FM, Moran CG, Pinder IM, Smith IR. The incidence of fatal pulmonary embolism after knee replacement with no prophylactic anticoagulation. J Bone Joint Surg Br 1993;75:940-1.
6. Ansari S, Warwick D, Ackroyd CE, Newman JH. Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases. J Arthroplasty 1997;12:599-602.
7. Klement P, Carlsson S, Rak J, et al. The benefit-to-risk profile of melagatran is superior to that of hirudin in a rabbit arterial thrombosis prevention and bleeding model. J Thromb Haemost 2003;1:587-94.
8. Johansson LC, Frison L, Logren U, Fager G, Gustafsson D, Eriksson UG. Influence

of age on the pharmacokinetics and pharmacodynamics of ximelagatran, an oral direct thrombin inhibitor. Clin Pharmacokinet 2003;42:381-92.
9. Eriksson UG, Johansson L, Frison L, et al. Pharmacokinetics (PK) of melagatran (M) in young and elderly healthy subjects and orthopaedic surgery patients. Clin Pharmacol Ther 2001;69(2):P24. abstract.
10. Eriksson UG, Fager G, Eriksson-Lepkowska M, et al. Effect of acetylsalicylic acid (ASA) on the pharmacodynamics and pharmacokinetics (PK) of melagatran (M), active form of the oral direct thrombin inhibitor, H 376/95. Clin Pharmacol Ther 2001;69(2): P24. abstract.
11. Eriksson-Lepkowska M, Thuresson A, Bylock A, Frison L, Eriksson UG. The effect

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of the oral direct thrombin inhibitor, ximelagatran (pINN, formerly H 376/95), on the pharmacokinetics of diazepam in healthy male volunteers. In: Proceedings of the 28th Congress of the International Society on Thrombosis and Haemostasis, Paris, July 6–12, 2001. abstract.

12. *Idem.* The effect of the oral direct thrombin inhibitor, ximelagatran (pINN, formerly H 376/95), on the pharmacokinetics and pharmacodynamics of diclofenac in healthy male volunteers. In: Proceedings of the 28th Congress of the International Society on Thrombosis and Haemostasis, Paris, July 6–12, 2001. abstract.

13. Johnasson S, Bylock A, Eriksson-Lepkowska M, Thuresson A, Frison L, Eriksson UG. The effect of the oral direct thrombin inhibitor, ximelagatran (pINN, formerly H 376/95), on the pharmacokinetics of nifedipine in healthy male volunteers. In: Proceedings of the 28th Congress of the International Society on Thrombosis and Haemostasis, Paris, July 6–12, 2001. abstract.

14. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind trial. Ann Intern Med 2002; 137:648-55.

15. Heit JA, Colwell CW, Francis CW, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. Arch Intern Med 2001;161: 2215-21.

16. Eriksson BI, Agnelli G, Cohen AT, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. Thromb Haemost 2003;89:288-96.

17. Eriksson BI, Bergqvist D, Kälebo P, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous throm-

boembolism after total hip or total knee replacement: the METHRO II randomised trial. Lancet 2002;360:1441-7.

18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

19. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg 1972;104:134-44.

20. Kälebo P, Ekman S, Lindbratt S, et al. Percentage of inadequate phlebograms and observer agreement in thromboprophylactic multicenter trials using standardized methodology and central assessment. Thromb Haemost 1996;76:893-6.

21. Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty — a meta-analysis. Thromb Haemost 2001;85:940-1.

22. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty: the RD Heparin Arthroplasty Group. J Bone Joint Surg Am 1994;76:1174-85.

23. Heit JA, Berkowitz SD, Bona R, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Thromb Haemost 1997;77:32-8.

24. Fitzgerald RH Jr, Spiro TE, Trowbridge AA, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am 2001;83:900-6.

25. Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. N Engl J Med 1993;329:1370-6.

26. Hamulyak K, Lensing AWA, van der Meer

J, Smid WM, van Ooy A, Hoek A. Subcutaneous low-molecular-weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Thromb Haemost 1995;74: 1428-31.

27. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of venous thromboembolism after knee arthroplasty: a randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med 1996;124:619-26.

28. Francis CW, Pellegrini VD Jr, Leibert KM, et al. Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement. Thromb Haemost 1996;75:706-11.

29. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305-10.

30. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833-40.

31. Mesko JW, Brand RA, Iorio R, et al. Venous thromboembolic disease management patterns in total hip arthroplasty and total knee arthroplasty patients: a survey of the AAHKS membership. J Arthroplasty 2001;16:679-88.

32. Gross M, Anderson DR, Nagpal S, O'Brien B. Venous thromboembolism prophylaxis after total hip or knee arthroplasty: a survey of Canadian orthopedic surgeons. Can J Surg 1999;42:457-61.

33. Hirsh J, Dalen J, Anderson DR, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001;119:Suppl 1:8S-21S.

34. Ansell J, Hirsh J, Dalen J, et al. Managing oral anticoagulant therapy. Chest 2001; 119:Suppl 1:22S-38S.

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